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Egg and milk exposure during pregnancy and food reactions in grandchildren

To the Editor,

The origins of food allergy and food-related symptoms are to a large extent not understood, despite their large impact on public health.[1] Our aim was to evaluate whether avoidance of intake of egg and milk during the last trimester of pregnancy compared to a high intake, associate to food reactions and IgE sensitization against egg and milk in the exposed woman's grandchildren.

The KUG (*Kost under graviditet*, 'Diet During Pregnancy') study was initially an open-label randomized trial with the intervention conducted between 1983 and 1985,[2] with the aim to study whether egg and milk exclusion prevent allergic disease in the offspring. The included study population were pregnant women with a history of bronchial asthma and/or rhino-conjunctivitis when exposed to animal dander and/or tree or grass pollen. They were randomized to a diet avoiding egg and milk (avoiding group) or a diet containing 1 egg and 0.5 L of milk per day (exposed group) during the last trimester of pregnancy.[3,4] Over 30 years later, 78 grandchildren were examined by a study physician, reactions to egg or milk ever were parental-reported and IgE against egg and milk measured (detailed method in Appendix S1). The avoiding group ($n = 27$) had 52 grandchildren and the exposed group ($n = 19$) 26 grandchildren, Figure 1.

There were no significant differences in baseline characteristics between the grandchildren from the two exposure groups Table 1.

We found a higher prevalence of reported reactions to egg among the grandchildren in the avoiding group $n = 8/52$ (15%) compared to the exposed group 0/26 (0%), $p = .047$. There was also a higher prevalence of reported reactions to egg and/or milk in the avoiding group $n = 16/52$ (31%) than in the exposed group $n = 1/26$ (3.9%) ($p = .008$). All participants who reported reactions to egg or milk with simultaneously elevated IgE belonged to the avoiding group, Table 1. The prevalence of atopic dermatitis was 24% in the avoiding group compared to 8% in the exposed group, although not a significant difference, however, could this suggest a higher risk in this group for food reactions.

In stratified analyses, the association between avoidance of egg and milk and higher prevalence of reactions to milk or egg and/or milk was present for maternal grandmothers' grandchildren but not for paternal grandmothers' (Figure S1A,B).

In the second generation, no participant in the exposed group reported reactions against egg or milk at 5 years of age (although no significant differences between the groups; Table S1).

Five women from the first generation with included grandchildren did not follow the analysis per protocol, two in the avoiding group and three in the exposed group, however, not affecting the associations (Table S2). Including only the oldest child from each family did not affect the associations either (Table S3).

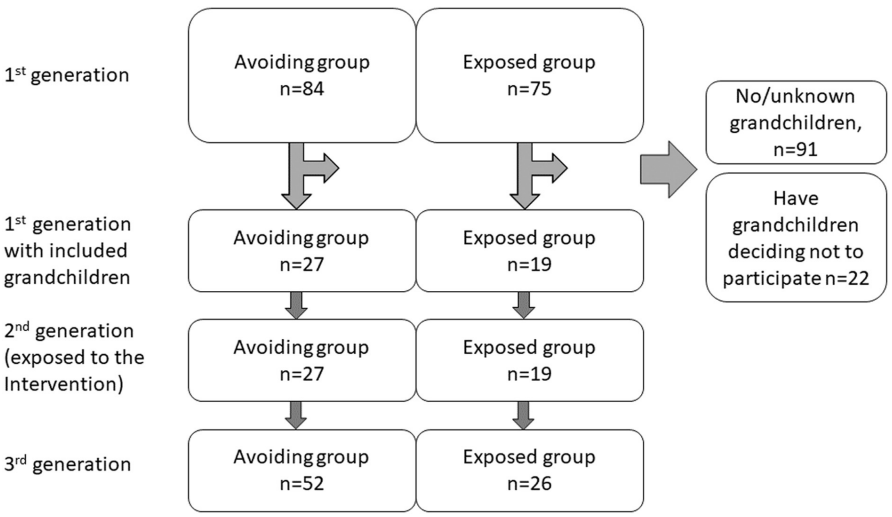

FIGURE 1 Flow chart of included population. The participants without grandchildren or whose grandchildren did not participate ($n = 113$) were excluded from the investigation. *n*, number of participants in each group from the respective generations.

TABLE 1 Background characteristics and prevalence of symptoms and elevated IgE against egg or milk in the third generation

Intention to treat	Avoiding group, *n/N* (%)	Exposed group, *n/N* (%)	*p*-value
Background characteristics			
Male sex	24/50 (48%)	16/25 (64%)	.19
Age[a] months median (IQR), min-max	*n* = 41, 43 (21–71), min: 6, max: 187	*n* = 24, 25 (18–51), min: 6, max: 129	.24
Age under 1 year	8/41 (20%)	5/24 (21%)	.90
Smoke exposure in utero	3/52 (5.8%)	1/26 (3.9%)	1.0
Smoke exposure after birth	7/52 (13%)	3/26 (12%)	.81
Exclusive breastfeeding ≥4 months	30/50 (60%)	15/25 (60%)	1.0
Symptoms			
Reactions to egg	8/52 (15%)	0/26 (0%)	**.047**
Reactions to milk	10/52 (19%)	1/26 (3.9%)	.089
Reactions to egg and/or milk	16/52 (31%)	1/26 (3.9%)	**.008**
IgE against egg ≥0.1 kUA/L	12/39 (31%)	3/23 (13%)	.14
IgE against milk ≥0.1 kUA/L	12/39 (31%)	6/23 (26%)	.78
IgE against egg and/or milk ≥0.1 kUA/L	18/39 (46%)	7/23 (30%)	.29
Egg: reactions and IgE ≥0.1 kUA/L	4/39 (10%)	0/23 (0%)	.29
Milk: reactions and IgE ≥0.1 kUA/L	3/39 (7.8%)	0/23 (0%)	.29
Atopic dermatitis	12/50 (24%)	2/25 (8%)	.12
Asthma	12/52 (23%)	4/26 (15%)	.56
Any food reaction	20/52 (38%)	7/26 (27%)	.45

Abbreviations: IQR, interquartile range; n, number in subgroup; N, total number.

[a]All participating children were over 6 months of age although the age was not recorded for all participants. Significant results in bold.

Not all children with ever-reported reactions had IgE against egg or milk. Reasons for this could be the wide age range, where some children might have grown out of their allergy,[5] and IgE only being tested in a subgroup. Others might react due to other mechanisms.

The association was only present for the maternal grandmother's grandchildren, possibly suggesting epigenetic mechanisms attributed to changes in the foetal oocytes to be at play, previously seen in studies on smoking.[6]

In conclusion, we found the lowest prevalence of egg and milk reactions in children whose grandmother did eat a diet rich in egg and milk during the third trimester of pregnancy. Despite a limited number of participants, our results suggest diets excluding food items, especially containing allergens, to be potentially associated with food reactions in later generations.

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KEYWORDS

environment and hygiene hypothesis, food allergy, food hypersensitivity, pregnancy, prevention

CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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The impact of dupilumab treatment on SARS-CoV-2 T cell responses in atopic dermatitis patients

To the Editor,

Studies on the pathophysiology of immune responses in COVID-19 point at a critical role for Th1 cells in viral clearance. Therefore, it has been postulated that abnormally elevated Th2 cytokines in individuals with atopic dermatitis (AD), a dermatological condition characterized by Th2-driven skin inflammation, impairs appropriate Th1 responses to viral infection and that specific Th2-targeting therapies are corrective.[1] In line with this hypothesis, we previously showed that dupilumab, a monoclonal antibody that blocks the IL-4Rα subunit, thereby inhibiting Th2-associated IL-4 and IL-13 signaling, is associated with milder COVID-19 severity in AD patients.[1] Importantly, dupilumab does not affect SARS-CoV-2 IgG antibody levels after vaccination.[2] However, the effect of dupilumab on T cell responses after infection or vaccination is not known.

We prospectively collected PMBC samples from ≥12 year old moderate-to-severe AD patients either after COVID-19 infection or after SARS-CoV-2 mRNA vaccination in the Department of Dermatology at the Icahn School of Medicine, New York, between June 2020 and October 2021. Fifty-five samples from patients with prior SARS-CoV-2 infection confirmed by positive anti-SARS-CoV-2 Spike IgG (unvaccinated at the time of sample collection), and 125 post-vaccination samples from different subjects were analyzed. PBMCs were incubated for 24 h with peptides covering the immunedominant regions of the S glycoprotein of SARS-CoV-2 and IFNγ and IL-2 antigen-specific responses were quantified using IFNγ/IL-2 Double-Color FluoroSpot (see Methods S1 and Figure S1 for further details). Spike antigens were used to provide comparisons between treatment groups as a measure of T cell responses for both post-infection and post-vaccination samples (the vaccine contains only spike antigen of SARS-CoV-2). Comparisons on $\log_{10}$-transformed spot counts to minimize the impact of outliers were made with unpaired Student's *t*-tests and correlations were calculated with the Spearman correlation coefficient. Patients were stratified into three cohorts based on their treatment strategy: (1) Dupilumab alone

Abbreviations: AD, atopic dermatitis; COVID-19, coronavirus disease 2019; IgG, Immunoglobulin G; mRNA, messenger RNA; PBMC, Peripheral blood mononuclear cell; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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